

EXOPHTHALMIC GOITRE

or

GRAVES' DISEASE,

by

H. W E I G H T O N, M.B., C.M, Edin.Univ., 1893.

Barnard Castle,
County Durham.

April, 1902.



The disease known as Exophthalmic Goitre, otherwise called Graves' Disease or Basedow's Disease, was recognised as a distinct affection of the human species early in the present century. Of late years, however, it has attracted a deal of attention from medical writers. Of late years also the function of that important organ of the body, the thyroid gland has to a great extent come to light, and its connection with Graves' Disease. Myxoedema and allied conditions more accurately defined. The exact part played by the thyroid gland in Graves' Disease is still a moot point, but it is generally admitted that whatever be the primary or initial cause of the disorder, an over-activity or perverted secretion of this organ must be the immediate cause of most of the symptoms.

Exophthalmic Goitre is a disease presenting three prominent characteristic features, namely:- exaggeration of the heart's action, protrusion of the eye-balls, and enlargement of the thyroid gland. Besides those symptoms there may be in more or less prominence, muscular tremor, nervousness and excitability, anaemia, dyspnoea, and others of less import.

ETIOLOGY: /

ETIOLOGY:

The Etiology of Graves' Disease as far as our knowledge goes is still imperfect. The disease mainly affects women, the proportion being variously stated by different observers. As large a proportion as twenty-eight females to one male has been given and again on the other hand a proportion of two females to one male has been stated. Probably some figure between those would be more nearly correct taking all districts into account, such as that given by Trousseau, namely:- six females to one male. In any case, it is well known that the proportion varies in different countries.

It occurs most frequently between the ages of twenty and thirty years, but examples of the disease have been known at the early age of two and a half years and so late in life as that recorded by Stokes, namely, at sixty years of age.

The disease is generally an insidious one, but one case had been observed by Trousseau to develop very marked and typical symptoms in four days. Since then, other writers have also remarked like cases. The disease may occur in several members of the same family. Oesterricher recorded the case of a nervous woman who had ten children, eight of whom suffered/

ed from Graves' Disease. One of those eight had three children all of whom developed the disease. This would tend to show that not only is the disease apt to occur in different members of the same family, but also that it may manifest itself in a succeeding generation. In most cases no cause can be assigned as the starting point of the disease, but in others again, it has been noticed to follow on fatigue, fright or great mental shock. Influenza also has been noticed to be a forerunner of Graves' Disease. Perhaps the most common cause given by patients themselves as a starting point of the malady is that of sudden fright. It is a matter of great interest to mark that the signs of a well marked case of this disease correspond in a great measure with the more usual signs or manifestations of great fear:- rapid action of the heart, throbbing of the vessels of the neck, trembling of the whole body, a staring condition of the eyes, and cold perspiration. On this observation it has therefore been argued that enlargement of the thyroid gland of the neck is not the primary cause of the disease called Exophthalmic Goitre, but rather that it is a condition following on an alteration or disturbance of the nervous system which produces and/

and perpetuates a certain train of symptoms. The malady is occasionally associated with other nervous manifestations particularly hysteria, chorea, epilepsy, or even insanity. Chlorosis is frequently existent at the beginning of an attack and may persist during the course of the disease. It has also been stated that extreme anaemia predisposes a patient to an attack of Graves' Disease, and Stokes quotes a case in support of this. This patient, a male, was the subject of haemorrhoids from which he had lost at various times a considerable quantity of blood. This man became extremely anaemic and ultimately developed Graves' Disease. Stokes was of opinion that in this case the anaemia was a predisposing cause of the disease. It has been noticed also to manifest itself during pregnancy or immediately after child-birth. It is also a well known fact that in a female, the subject of Graves' Disease, who has become pregnant, the malady undergoes a marked amelioration for the time being. Like tubercular disease, it affects all classes of society and is found in all countries. It is never really endemic in any part and is in that respect very different from ordinary Goitre, but at the same time, it may be found in many parts where ordinary Goitre exists./

exists. It has also been stated by some that derangement of the organs of generation may have something to do with the causation; but in contradiction of this again, it is found that the disease occurs more frequently in the unmarried than in the married. Quinsy and rheumatism have been noticed as frequently accompanying the disease, but the number of cases are not numerous.

MORBID ANATOMY:

In the cadaver emaciation is the most prominent feature noticeable. The exophthalmos is not so marked after death as during life. The thyroid enlargement persists after death. In a great many cases it is somewhat interesting to notice that the thymus gland is also hypertrophied, while in other instances again, there may be no apparent alteration as regards size. The spleen also is occasionally found enlarged. In the nervous system nothing of importance may be found; even the sympathetic nervous system which has been mentioned by some as the primary factor in the causation of the disease, is generally found in its normal condition.

The heart often suffers to some extent in any long-continued case of Graves' Disease. There will generally be found a dilatation or hypertrophy of this/

this organ and occasionally, but rarely, it is the seat of valvular disease. In some cases however, the heart has been found to be almost normal. The lungs are generally not affected unless from accidental complications such as pleurisy or pneumonia.

As regards the thyroid itself, it is oftenest uniformly enlarged. In an occasional instance, however, it may present a nodular appearance. In consistence it is firm, and on section, of lighter colour than the normal gland, and exudes less colloid material. If nodular swellings are present, they will be found to consist of firm fibrous tissue, enclosing a small amount of colloid material. It has been found that the whole gland is very vascular. This, however, is not a constant condition, and is even denied by some who hold that the vascularity is chiefly superficial. The blood vessels of the gland are generally dilated and tortuous, the veins having very thin walls. It is a matter of general concession however, that the vascularity of the thyroid in Graves' Disease exceeds that of any other variety of Goitre. The microscopical appearance of the glands structure is consistent with a condition of exaggerated activity, hence it is not difficult to imagine that the vascularity increases accordingly/

cordingly. Under the microscope a leading feature in the gland structure, even in a comparatively early stage of the disease, is the increase of the number of tubules and an alteration and proliferation of the epithelial lining. So great a proliferation has been recorded as to project into the gland spaces. The cubical epithelium becomes to a great extent columnar and the lumen of the tube becomes diminished in size. The colloid material in the gland spaces is always diminished in quantity and has even been said to have been absent altogether in certain cases. Where it does exist, it is more watery than in the normal gland and stains more deeply. There are two explanations which naturally occur to account of this diminution or absence of colloid material;- it may be that the fibrous tissue encroaches on the colloid space and thereby prevents its accumulation, or it may be that the material is used so quickly in Graves' Disease, that none can be stored up. *Professor Greenfield has pointed out the occurrence of new tubular spaces lined by cubical epithelium, these tubules resembling to some extent those of a secretory gland. The same authority has also pointed out that the thyroid gland in Graves' Disease resembles in structure that of/

* Lancet, December 1893.

of a salivary gland and further, that the thyroid during the course of this disease bears the same relation to the normal gland as does the mammary gland during lactation to the same organ in its quiescent state.

The thymus, as has already been said, generally persists to a greater or less extent in Graves' Disease. Its microscopic structure, however, remains unaltered.

Minute haemorrhages have been remarked to occur in the medulla. Those also have been noticed in cases of myxoedema and are consequently considered to be of no importance. Changes have also been said to occur in the floor of the fourth ventricle, but those are also likely to be of accidentally occurrence. The muscular tremor in Graves' Disease has been explained by Askanszky as due to a severe and widespread alteration in the voluntary striped muscles of the body. These muscular lesions would account for the clinical symptoms shown in loss of flesh, loss of strength and paraparesis of the legs described by Charcot. Also, it would account, Askanszky says for the exophthalmos, the sign of moebius and the later bulbar symptoms.

PATHOLOGY:

A great many theories have from time to time been brought forward by various observers to account for the curious train of symptoms occurring in Graves' Disease. The circulatory system has been found fault with, the blood itself has been blamed and also the nervous system, and especially the sympathetic nervous system has received attention as likewise has the digestive system. It is true that various lesions occur in the central nervous system in Graves' Disease, but some of those also have been noticed in connection with myxoedema, and must therefore only be of secondary importance; in fact, they may be accidental. It is probable, however, that certain lesions of the central nervous system such as an interference with certain centres in the medulla would produce an alteration of the thyroid gland and consequently, all the symptoms of the disease. * Dr W. H. Thompson considers that a paralytic lesion of the common nucleus of the Glosso-pharyngeal, vagus and spinal accessory nerves and extending to the neighbouring vaso-motor centres in the medulla would account for all the phenomena of the malady. This theory may be almost borne out by the various eye symptoms, such as von Graefe's sign, Shellwag's sign, /

* New York Medical Journal, March 1893.

sign, defective convergence, etc. Von Graefe's sign must be of the nature of a want of co-ordination of movement. These facts, however, do not actually prove the nervous origin of the disease although they somewhat strongly support it. Some of the symptoms could also be accounted for by a lesion or lesions of the sympathetic ganglia, but it seems impossible to account for others, or form a theory from this cause alone. The widespread nature of the symptoms is opposed to this view, as is also the fact that a constant alteration of the sympathetic has never been found to be present. In favour of the sympathetic theory, it has been found in some cases that section of those nerves has resulted in amelioration, if not cure of the disease, but this is by no means a constant occurrence. According to*Gowers the sympathetic theory is untenable. He says that it involves a double action, firstly, a partial affection, and secondly, a twofold action. It involves a stimulating action on the accelerating fibres in connection with the heart and simultaneously, a paralysing action on the vaso-motor fibres, which, as he says, is a double-barrelled action, the probability of which is rather remote. Further, if the sympathetic is affected/

* Diseases of Nervous System, Vol. II.

affected one would expect the pupils would be dilated, an occurrence which is very rare indeed.

The thyroid gland itself is the most constantly affected organ in connection with Graves' Disease. There is now no doubt that an over secretion and along with this, probably a perverted secretion of the gland, would account for the symptoms of the disease, but whether the disease begins and ends with an initial lesion of this organ, or whether this condition of the thyroid is secondary to some other phenomenon as yet unsettled, is a matter for further investigation. It might be possible that by means of the hypertrophy of the secreting element of the gland structure and consequently, an increased secretion, a larger quantity than normal of this is thrown into the blood stream. It might thereby exert an action on the tissue metabolism of the body generally, on the nervous centres in particular in the medulla, and produce all the phenomena recognised as Graves' Disease. But again, if this were so, it would be possible to produce the disease artificially by feeding with thyroid substance, This, however, has not been attained, but if, as is asserted, the normal secretion is altered in some way as yet not explained, this artificial production of/

of the disease would not occur. All this again is merely theory and cannot be substantiated. It is now well known that the opposite condition exists in myxoedema namely, a diminished secretion or absence altogether of thyroid secretion. It is only necessary to contrast the general phenomena of the two diseases to show that if in the one, the immediate cause of the disease is a want of secretion, in the other, the cause would naturally be an exaggerated secretion. In myxoedema there is found the swollen oedematous-like condition, the slow pulse rate, the subnormal temperature, the dryness of the skin and great increase of electrical resistance, constipation and general stolidity, whereas in Graves' Disease the patient is generally emaciated, the pulse greatly increased in frequency, the temperature elevated, the skin moist and often bathed in perspiration with a greatly diminished electrical resistance, looseness of the bowels and general nervousness.

It is interesting to note also the fact that Exophthalmic Goitre has been frequently followed by Myxoedema, whereas Myxoedema has never been recorded as having been followed by an attack of Graves' Disease. In explanation of this, it is probable that/

that as the fibroid condition of the thyroid gland increases in Graves' Disease, the secretion becomes firstly normal in quantity and later diminished, so that a myxoedematous condition supervenes.

All this therefore only goes to show that the immediate cause of the whole disorder is in all probability a larger quantity than normal of the secretion of the Thyroid gland in the system, or as some authorities have argued an altered or perverted secretion or perhaps both. Over and above this, it is now generally believed that some lesion in the nervous system probably in the medulla is the true starting point of the disease. It has been held that Exophthalmic Goitre is entirely the direct result of the hysterical neurosis. This hysterical condition, it is said, is sufficient to produce a thyroid intoxication which would ultimately lead to changes in the general system producing all the symptoms of the disease. This theory, however, is a very unlikely one. It is difficult to imagine in the first place that the neurosis would produce such an increased amount of secretion as to cause an intoxication, and secondly the increase would in all probability have to be a constant one. Again, it has/

has been advocated that the absorption of a poison from the intestine might be the fundamental cause of Graves' Disease. *Thompson of New York was at one time of this opinion and treated the disease chiefly by dieting and intestinal antiseptics. If we consider the various diseases which are now generally believed to be caused by a toxin, it will be at once admitted that until our knowledge of the pathology of Graves' Disease is more exact, this theory certainly deserves a place amongst the possibilities. Pernicious anaemia is now generally accepted as being caused in the first place by the absorption of an intestinal toxin, which destroys the blood corpuscles. Hodgkin's Disease and also Leukaemia may be also looked upon as originating from some poison as yet unclassified, finding its way into the blood.

In support of this poison theory, as has been pointed out by**Carter, we have only to consider those few cases on record in which all the symptoms of Graves' Disease have appeared in an alarmingly short space of time and have ended fatally; one even on the third day of illness. And lastly of all, there is the miasm theory that it is a disease peculiar to certain parts of a country, and allied in/

* American Journal of Medicine Science, Feb. 1897.

** Edinburgh Medical Journal, Oct. 1899

in a certain degree to the simpler endemic form of goitre. It has been said by certain observers that some parts of this country produce more instances of the disease than others, and also that in some of those parts where endemic goitre is prevalent, more cases of Graves' Disease are forthcoming than in those parts where the endemic form is absent. This, however, is probably not correct as the writer has lived in a district in Monmouthshire where the endemic form of goitre is extremely prevalent, and no case of Graves' Disease came under his notice during nearly two years' stay in that locality.

SYMPTOMS:

These are generally well marked and easily recognisable. There are, however, a certain number of cases in which the symptoms may be considerably modified, thereby rendering an early diagnosis somewhat uncertain. It was at one time considered that there were three cardinal or primary symptoms in Graves' Disease, namely, exaggeration of the heart's action, enlargement of the thyroid gland and protrusion of the eye-balls. To these, however, may safely be added as primary symptoms in a typical case, muscular tremor and general nervousness.

The/first t...

The first symptom which attracts the patient's attention and probably sends her to a medical man, is the palpitation. The Thyroid enlargement may be also present, but as a rule is not noticed by the patient until pointed out. The exophthalmos may also make itself manifest at the beginning of the disease, and advice is sought for this. Then irritability and nervousness very soon become apparent, and more gradually perhaps the peculiar muscular tremor. It is not by any means necessary to have all the cardinal symptoms together in one case to form a diagnosis of Graves' Disease. Sometimes for instance, the thyroid enlargement may be absent in a well established case, or at least it may not be apparent. In others again the exophthalmos may not make itself manifest. The cardiac irritability, however, is the most constantly present symptom in the disease. In a case at present under observation, the most prominent symptom is a considerable degree of exophthalmos. There is also great nervousness and some degree of emaciation, but no apparent enlargement of the thyroid gland. This case has been pronounced by a good authority to be one of an irregular form of Graves' Disease.

EYE SYMPTOMS:

As has already been pointed out, the exophthalmos may be very slight in degree. It varies greatly in different cases. In other instances again it may be so great that the eyelids are unable to cover the eyeballs. In such cases, there is a tendency to inflammation and ulceration of the cornea leading perhaps to entire destruction of the eye. *Dr George Berry holds that there may be an anaesthesia of the cornea in some cases of Graves' disease. If this is so, it would tend to favour an early ulceration. In certain cases also, the insertion of the recti muscles can be seen. As a general rule the exophthalmos is bilateral, but cases of unilateral exophthalmos have been recorded. These are, however, of rare occurrence. An oedematous or glistening condition of the eyes is not uncommonly present. A peculiar condition with regard to the movements of the eyeball and its upper lid, first pointed out by von Graefe and generally known as von Graefe's sign, has been long recognised in this disease. This sign may be very easily demonstrated by holding the finger before the patient's eyes and instructing her to follow the movements of the finger with the eyes. As the eye moves/

*Text-book, Diseases of Eye.

moves upwards and downwards it will be found that the eye-lid does not follow the eye so exactly as in health. There is a tardiness of the lid in following when the eye is rotated downwards, so that a greater amount of schlerotic can be seen than is the rule in the normal eye. Evlanberg has, however, found this sign absent in very pronounced exophthalmos. It has been claimed also that von Graefe's sign has been noticed in other conditions besides Exophthalmic Goitre. Another sign of some importance is that bearing the name of Stellwag who first described it. This consists of an increase or enlargement of the palpebral fissure of the eye, formed by a retraction of the upper lid, and in that way showing the schlerotic above the cornea. This retraction of the upper lid is of very common occurrence in Graves' Disease although not constant, and is supposed to result from a spasmodic contraction of Muller's Muscle. This symptom has not been noticed in any other condition but Graves' Disease. An appearance very similar is produced when cocaine is applied to the eye.

Yet another eye symptom although not so constant as the two just described, is that going by the/

the name of Mobius' Sign. This consists in an insufficient power of convergence for near objects. There is, however, no double-vision, but a considerable strain is necessary in order to bring the object into focus.

As a rule, however, the power of vision in Graves' Disease is but little altered. Various other symptoms may occasionally be present such as a fullness or feeling of weight in the eyes, flashes of light before them, or sometimes fatigue in using them. Another condition which may occasionally be present in an Ophthalmoplegia externa or paralysis of the external Recti muscles. In this condition there would be double vision on attempting to look to the extreme left or right. A fatty degeneration has been found in those muscles, but this again might be accounted for from the great stretching which they undergo, but why of the external muscles only it is difficult to say.

Complete dislocation of the eye is of rare occurrence but has been known to take place. This might be caused by a sudden spasm of the orbicularis muscle. A boggy oedematous-like condition has frequently been remarked in the upper or lower or even both eyelids. It does not pit on pressure and is therefore evidently not a true oedema, and also it has/

has been known to practically disappear on the application of electrical stimulation to the orbicularis muscle. It is oftenest chronic in its nature and even remains after most of the other symptoms of the disease have disappeared.

On ophthalmoscopic examination the veins of the retina are somewhat dilated and tortuous. The retinal arteries have also been noticed to pulsate.

The pupils in some cases have been noted as generally enlarged. This however is not a constant condition by any means, and may be due, as has been pointed out, to a previous or acquired myopia. As to the cause of the exophthalmos, various conditions have been considered. Three causes may be mentioned as likely to produce the condition, namely:-- increase of the orbital fat, engorgement and dilatation of the orbital vessels or contraction or spasm of Muller's non-striated orbital muscle. The exophthalmos has been noticed to vary with the condition of the heart; being more pronounced when the heart is greatly exaggerated in action. An increased fulness of the eyes has been complained of by women suffering from the disease during the menstrual epoch. It is rather remarkable to note that after death the prominence of the eyes almost entirely disappears.

In/

In an occasional case a total or almost total absence of exophthalmos may be noted as the following case will show. In January of this year a man aged 45 was seized with an acute attack of influenza. There was considerable temperature for a few days and then a gradual return to normal. The pulse was very rapid during the stage of pyrexia, but on the temperature returning to normal the pulse rate did not alter to any great extent and still remains at a rate of 120 to 130 or occasionally more. Muscular tremor then made itself apparent as did also a condition of extreme nervousness. This man has been the subject of an enlargement of the thyroid for many years, but gave him no inconvenience whatever. There is now, however, distinct throbbing over the gland, but no hum that is appreciable. The other organs are healthy. The remarkable feature of this case is the entire absence of exophthalmos or other eye phenomena. The eyes have a slightly staring appearance but it may be that this is his normal condition. He always had a slightly prominent eye. This case is also remarkable from the fact that Graves' Disease has apparently supervened in a man the subject of a simple goitre which has existed for many years.

used a distinct hum may be heard, similar to the venous bruit in anaemia. The pulsation is however most distinct over the carotid arteries. This has been called the "hammering carotids". A haemic sort of murmur may also be heard over the veins of the neck. The enlargement of the thyroid is not always constant, but may vary somewhat in size during the course of the disease. An alteration in size has also been noticed during emotional excitement or after exertion. It has been already stated that the enlargement is never great in Grave's Disease, in fact it may be so slight as not to call for notice until it has been specially looked for. The patient may however find it out herself, generally from the dress failing to meet round the neck. In some instances again, the enlargement has been so great as to seriously threaten the passage of air through the trachea, and more so is this the case on even slight exertion.

It has also been found that from long-continued pressure on the trachea it has become flattened and altered in shape. Dr Wilks makes mention of one case where the enlargement extended down into the thorax and produced an obstruction of the thoracic duct.

THE/

THE HEART AND CIRCULATORY SYMPTOMS:

In the whole circulatory system the symptoms of greatest importance are those of the heart itself. The heart's action is generally greatly accelerated; in very few instances is it only slight, although this has been noticed. This tachycardia is the most constant symptom in Graves' Disease. Most usually the rate varies from 100 beats per minute to 130, but occasionally it reaches 180 or more. The rate varies a great deal during periods of excitement, when it is always more exaggerated than usual. The patient is generally well aware of this constant palpitation of the heart, but in a few cases where the palpitation is not of great degree they may not be aware of it. The latter condition, however, is rare. The palpitation is very often regular in rhythm, but under certain circumstances it may become very irregular. It is somewhat of importance to know that if a pulse for a period of a longer or shorter time has been greatly accelerated and gradually begins to fall in the number of beats, it forms the best sign we know that improvement is taking place. In a case under treatment therefore it becomes a very good guide as regards prognosis.

On examination the beating of the heart can generally be very distinctly seen, especially since the/

the subjects of Graves' Disease are somewhat emaciated or at least very thin. It is even said to be possible to hear the sounds of the heart at some distance from the patient, and Graves claims to have heard them at a distance of four feet. Some degree of prominence may also be apparent in the praecordial region. The cardiac sounds when no disease exists are sharp and somewhat accentuated. In those conditions of greatly increased heart's action it is only natural that dilatation or what is perhaps more rare, hypertrophy may occur. It is a remarkable fact, however, that valvular organic disease is of rare occurrence.

A systolic murmur can occasionally be heard at the mitral or pulmonary areas and less frequently at the others. Systolic murmurs at the mitral or tricuspid openings might be accounted for, from dilatation of the ventricles.

Hammering of the carotid arteries in the neck, as has been pointed out, is a very constant condition in Graves' Disease. Patients have also complained of a pulsation in the abdominal aorta, in fact a throbbing has been complained of all over the body. Fulness of the veins of the neck is very often noticed, and haemic or blowing murmurs can also be heard in this region.

The/

The cause of the accelerated heart's action is not yet distinctly settled. Some have said it is an undue stimulation from the cervical sympathetic, and others again that it results from a diminished action of the vagus. Which of these is most likely or whether they both play a part is still a moot point.

THE NERVOUS SYSTEM:

One of the chief symptoms in connection with the nervous system and one which is now looked upon as a cardinal symptom of the disease, is that of muscular tremor. This symptom was probably first described by Basedow, and afterwards more particularly perhaps by Marie and by Charcot.

The tremor consists of fine rhythmic muscular movements varying from eight to nine per second. It is found that this rapidity of tremor is about twice as great as that in paralysis agitans, which number four to five per second.

It mainly affects the limbs, but may be noticeable over the whole body. In some cases it is most apparent in the arms, and sometimes in one arm more than another. The tremor also varies in degree in different cases. In some it may be almost altogether wanting, while in others it may be the most prominent/

minent symptom of the disease. Like the heart symptoms if the patient is in any way in an excited condition the tremor will be very much more marked than under ordinary circumstances. It may be also more marked when the patient is standing than when in the recumbent position. Tremor is not usually perceived until the other important symptoms of the disease are developed, but this is not always the case, as it has occasionally been noticed very early in the disease.

Cramps of a painful nature sometimes make themselves apparent in the hands and feet and particularly in the fingers or toes, and this is perhaps more frequent during the night. As a rule those cramps are of a temporary nature, but a spasm of the nature of a tetany has been remarked. Weakness of the knees with a constant tendency to fall down has been frequently seen during the course of Exophthalmic goitre. On the slightest exertion the knees tremble and the patient feels in a condition of being extremely tired.

General excitability and nervousness is a very characteristic symptom of the disease. A very small matter "puts them about". A change in the mental condition of the patient occurs early in the disease. They become irritable, changeful, dissatisfied and constantly/

constantly longing for changes and novelties. At one time the patient may be satisfied and happy and at another time low spirited and even melancholic. Mania may even occur, and when it does take place the case may be looked upon as serious indeed. It is rather remarkable that the sufferer from Graves' Disease is very rarely hysterical, or if so it shows itself late in the disease, probably when the symptoms begin to subside. Headache is very frequently complained of by patients, and also various neuralgias are somewhat common. The tendon reflexes are generally present, and in some cases they may be slightly exaggerated.

INTEGUMENTARY SYSTEM:

Pigmentation of the skin in various parts is somewhat common in Graves' Disease. This condition has received particular attention from Dr David Drummond of Newcastle. It is most common in those parts of the body normally endowed with pigment:- the areolae of the breasts and in the pudendal region. It may also occur in the face, and is sometimes well marked as a muddy or earthy appearance, or occasionally a bronzing condition. Patches of pigmentation are also common and may occur on the/

the face, neck or abdomen. The flexures of the arms and thighs are also common seats of this pigmentation. In some cases the pigmentation may limit itself to the eye-lids alone.

Leucoderma and Scleroderma have been also remarked, and it is somewhat of interest to note that Leucoderma has also been a frequent accompaniment of Addison's disease. Flushings of the head, face and neck are often complained of by sufferers from Graves' Disease, also sweating of the whole body or of parts of the body is often a prominent symptom, and especially has it been noticed to an uncomfortable degree in the hands and feet. It is a most common secondary symptom. Oedema of a temporary nature is frequent in various parts of the body and is liable to recur. Falling out of the hair is also a prominent symptom and has occurred to such an extent that a considerable alopecia has been recorded. This falling out of the hair may occur in any part of the body where hair naturally grows.

The temperature of patients suffering from Graves' Disease is liable to great variations. It is somewhat remarkable, however, that as a general rule the temperature is never very high, especially seeing that the patient always looks as if a high temperature/

temperature were present. This is looked upon generally as a subjective symptom. Patients generally prefer a cold atmosphere to a warm, as they are always more uncomfortable in a heated room. Elevations of temperature are said to be common during the menstrual period. A most remarkable fact in connection with the skin in exophthalmic Goitre is that the electrical resistance is diminished to a great degree. This might be explained by the fact that the skin is constantly bathed in perspiration, but it is found that in other diseases where the skin is also in a very moist condition, the degree of diminution is not so great as in this malady.

DIGESTIVE SYSTEM:

The appetite may be variously affected in different cases of the disease. While in one the appetite may be very poor indeed, in another a condition approaching bulimia may be present. However, in a great many patients the appetite suffers but little from the condition, or it may be limited to a preference for peculiar articles of diet. As one would naturally expect, anorexia is generally associated with extreme emaciation and cachexia. There is often a great craving for fluids in pronounced cases of Graves' Disease, and constant thirst/

thirst is often a prominent symptom. Vomiting is also occasionally a troublesome symptom. It appears in some cases to have no relation to the ingestion of food, while in others, food of any kind can not be tolerated in the stomach, but is immediately returned and at the same time the patient may suffer from severe epigastric pain and griping in the bowels. It has been remarked also that a periodic diarrhoea is of somewhat frequent occurrence. This may last for a few weeks at a time and disappear again for a like period or longer. If persistent, however, it is generally found to be of grave moment, and death has been known from exhaustion. This symptom like many others of a secondary nature, has been attributed to a perverted innervation. Vomiting and diarrhoea may occur together. Emaciation, as has already been said, is the general rule in Graves' disease, and is sometimes very extreme. This again is, and may become an important feature as regards prognosis. It is often found that if a patient becomes less emaciated, or in other words, if she puts on flesh, it forms a tolerably good sign that the disease is probably abating. It has been recorded that in the milder forms of the disease, emaciation may not be at all well marked, and in fact, isolated cases are on record where the opposite condition/

condition has existed throughout without much change. This is, however, somewhat rare.

RESPIRATORY SYSTEM:

The chief symptom in connection with this system is probably that of dyspnoea. As a rule, it is of a periodic nature and generally associated with other periodic symptoms such as extreme palpitation of the heart, flushing of the face, fulness of the neck vessels, cyanosis and occasionally threatened asphyxia. These attacks have been known to produce death.

Another symptom of note is the occurrence of a short and often dry cough, probably sometimes of a nervous origin. This, however, is sometimes present in other goitrous diseases.

A symptom occasionally met with, but not at all constant, is that going by the name of Bryson's Symptom. This consists of a diminution in the expansion of the chest at each inspiration. This was first described by Dr Louise Fiske Bryson in 1889, and named after her. In a number of cases recorded by her, this symptom was present in a large percentage, and in one case in particular, the expansion on forced inspiration measured only a quarter of an inch. In a case quoted by Dr Bramwell* death occurred/

* Anaemia and Diseases of

Glands, p.400.

red from pulmonary oedema accompanied by a profuse bronchial secretion. This, he attributed to a vaso-motor paralysis comparable to the profuse sweating and copious diarrhoeas common in the disease.

RENAL SYSTEM:

In many cases there is polyuria and an occasional glycosuria, or albuminuria. In cases of the latter condition there may be no tube casts present or other of the ordinary conditions found in Bright's Disease. These may all be due to vaso-motor derangements. If it is true that the medulla is affected in Graves' Disease it is not to be wondered at that many of these conditions are present.

REPRODUCTIVE SYSTEM:

There is generally considerable disturbance of the catamenial flow during the course of Graves' Disease in female patients. Irregularity alone may be present but there is often amenorrhoea, menorrhagia, or other symptoms. In many cases, however, the flow of the menses is little interfered with. It is always possible for the female patient to become pregnant and it has been remarked that in the later stages of the disease at least, improvement may take place, while in a pregnant state. It has also been noticed/

noticed that the disease may make itself apparent during the pregnant state.

HAEMATOPOIETIC SYSTEM:

Anaemia is somewhat frequent, especially in young people suffering from Graves' Disease. It is not however a constant symptom of the disease. It has been considered by some to be a frequent forerunner of the malady. Haemorrhages from various sources have been noticed but most frequently perhaps there is a tendency to epistaxis. Enlargement of the lymphatic glands and spleen have also been remarked.

DIAGNOSIS:

When the cardinal symptoms of the disease are at all well marked there is generally little difficulty in recognising Graves' Disease. Those cases however where one or more of the important symptoms are absent, or only slightly developed, there may be a considerable difficulty in diagnosis. The cardiac rapidity is the most important symptom, the other cardinal symptoms varying greatly in degree.

To confound Exophthalmic Goitre with the ordinary endemic variety is not at all likely, unless indeed it be in a highly nervous and hysterical patient. The size of the thyroid swelling is a point of great importance./

importance. In simple Goitre the swelling is often very large, whereas in Graves' Disease it is never so. In the latter malady also the throbbing and thrills felt over the enlarged gland is of great importance. Also there will be an entire absence of the heart symptoms (so characteristic of Graves' Disease) in an ordinary goitre and also the exophthalmos and peculiar tremor. It is possible that in some cases of simple goitre where the tumour is very much enlarged on one side, the sympathetic and vagus may become pressed upon or irritated. This might produce, it is said, a prominence of the eyeball on that side and perhaps also increased frequency of the heart's action. The unilateral eye condition, the presence of other symptoms of sympathetic derangement on that side, especially dilatation of the pupil, and the absence of many secondary symptoms of Graves' Disease will sufficiently serve to distinguish the two conditions. Protrusion of both eyes equally is a very unlikely condition in any other malady except Graves' Disease. There is seldom any sign of strabismus and the pupils are equal. Paroxysmal enlargement of the thyroid is pathognomonic of Graves' Disease.

The differential diagnosis of slight atypical cases of Graves' Disease from a simply functional rapidity of the heart's action is sometimes a matter of difficulty. The results of treatment will very soon/

soon assist the observer to form a diagnosis. Also the intermittent and paroxysmal nature of the palpitation in the functional variety compared with the persistent exaggeration in Graves' Disease will be of importance. Hysteria will probably be present in a case of simple functional palpitation whereas on the other hand it is remarkably rare in cases of true Graves' Disease. All doubt will generally be dispelled by carefully looking for the various and many secondary symptoms of Graves' Disease. The differential diagnosis from true disease of the heart gives generally little difficulty. Organic heart changes are somewhat rarely found in Graves' Disease, and the secondary symptoms must again be looked for.

PROGNOSIS.

A guarded prognosis must be the general rule in dealing with most cases of exophthalmic goitre. The termination is always uncertain. Some do terminate favourably after a shorter or longer period, but relapses are common and this tendency must always be kept in mind in giving a prognosis. In mild cases only is a favourable prognosis warrantable, and even then disappointments are not infrequent. Hulke has said (that it is a most definite and striking example of a severe and protracted malady which, despite its severity and persistence, has yet a natural tendency to recover.) This must be true to/

to a certain extent, as a good number of cases after several years it may be, in duration, get almost completely well. Some cases, however, although apparently well, are only to a certain extent recovered; some symptoms or consequences of the disease remaining permanent.

In 57 cases tabulated by*Ord and Mackenzie 24% ended fatally, 17% completely recovered and the others only partially recovered or remained "in statu quo". The same authorities give it as their opinion that 50% of all cases will eventually recover. This percentage is higher than that given by most authorities however.

*Byrom Bramwell states that one third or even one fourth is above the mark.. Perhaps in the near future the disease may be looked upon as more hopeful than at present, for the successes lately attained by some by surgical treatment and by others by the administration of thymus gland, warrant this prognostication. To arrive at a safe prognosis, the following conditions must be carefully looked to, namely, the condition of the pulse and the rapidity of the heart's action, the presence or absence of untoward complications, and the degree of emaciation/

* Allbut's System of Medicine, Vol.II., p.501.

* Anaemia and Diseases of Ductless Glands, p.416.

tion and power of absorbing nutrition.

As has already been said, a favourable prognosis may be given if the pulse shows signs of diminished rapidity, or if the patient begins to increase in weight.

COURSE AND DURATION:

The disease generally runs a chronic course, acute and rapidly terminating cases being somewhat rare. In those acute cases, lasting perhaps only a few days or perhaps several weeks, recovery may take place with like rapidity to the onset or what is perhaps less frequent, terminate rapidly in death. The shortest period of duration remarked, is that of two days, and this case completely recovered.*

Other two cases have been known to last only twelve days and six weeks respectively, and those also terminating in recovery. In the generality of cases, however, the general rule seems to be that the disease starts acutely and gradually assumes a chronic and lasting nature. Again in the course of a chronic case, acute exacerbation may occasionally take place. It is of great interest to note that myxoedema is a somewhat frequent sequel to Graves' Disease. Many instances of this have been reported from/

*

British Medical Journal, Vol. I., 1883.

from time to time, some in which the Myxoedema followed almost immediately on the cessation of symptoms of the Exophthalmic Goitre and in others, years after all the symptoms of the Graves' Disease have passed away. A rather peculiar admixture of those two diseases has been recorded by *Osler in which all the symptoms of Graves' Disease were present with toxæmia and mania but there being present also many of the signs of Myxoedema.

TREATMENT:

The treatment of Graves' Disease at the present day is still somewhat unsatisfactory. In the opposite condition - Myxoedema, where, as is now amply proved, there is a diminution or want of secretion by the Thyroid Gland, it is an easy matter to supply that want artificially. But in Exophthalmic Goitre in which the immediate cause is now believed to be an increased (or increased and perverted) secretion from the thyroid, it becomes a matter of much more difficulty to diminish the amount passed into the blood stream or even to regulate it in any way. The natural treatment which suggests itself is to exhibit some drug which would diminish the activity of the/

* Journal of Nervous and Mental Diseases, Feb. 1899.

the thyroid gland. By drugs alone, however, it has been found from long trial to be impossible. Again, another way in which this end may be attained, and which has received a deal of attention of late years, is that by dealing with the gland by surgical means; such as excision of part of the gland itself or ligation of certain of its arteries of supply. This form of treatment also has only procured a small measure of success. An easy way of getting rid of the disease that at once suggests itself, only to be put aside again as rather a severe measure, is to completely remove the thyroid gland, thus in time producing a condition allied to that of Myxoedema. This would necessitate the administration of thyroid extract for the rest of life, and seeing that Graves' Disease is one that, although severe and protracted, yet in many cases it tends to resolve and get well, the operation is altogether unwarranted. In any case of Graves' Disease, treatment by means of drugs and particular attention to the general surroundings of the patient ought to be the first consideration unless indeed there is immediate call for other forms of treatment. The patient should be kept free from everything likely to cause excitement. A little exercise may be indulged in if the condition of health/

health will permit, but absolute rest will most often be of benefit. Rest in bed is occasionally required, especially if the patient becomes very weak and debilitated. The diet must be simple and nutritious and chiefly farinaceous. Tobacco must on no condition be allowed and alcohol or tea very sparingly. If it is decided to treat a particular case by means of drugs and on general constitutional lines, the patient's friends must be warned that the progress must necessarily be slow, and perhaps at times apparently unsatisfactory. Treatment on those lines as *Dr Draper has said (and which still holds good at the present day) must be very variable and very comprehensive. The disease must receive treatment on general principles, and if any one line of treatment is decided upon, it must be followed up with determination. Belladonna is a drug which has received long trial in the treatment of Graves' Disease. In a great many instances, most appreciable benefit has been recorded from its use. It may be given in the form of the tincture beginning with minimum doses and gradually increasing till toxic symptoms show themselves.

Atropine has also been used with little effect. Bromide of Potassium will also be of service in controlling/

* New York Medical Review, July 11th, 1891.

trolling the nervous manifestations of patients, and in this way allow them a little confidence in the treatment. This may be given along with the belladonna. Phosphate of Soda has also been given a great deal in this disease and Kocher claims to have had good results from its use. Arsenic, Strychnine, Ergot of Rye, Iron and Digitalis need only be mentioned as having been given in order to allay the various symptoms. Iodides have also been extensively tried, but it has been found that some symptoms have been greatly exaggerated by their use. *In latent Graves' Disease where this treatment has been actively employed, a recrudescence of the disease has shown itself and which, on withdrawing the drug, the disease again returned to its former latent state. Again, Quinine has been reported as productive of great benefit. Paulesco and Reynier have chiefly advocated this line of treatment on the assumption that Exophthalmic Goitre is not caused by disease of the thyroid itself, but that it is caused by a general vaso-dilatation producing an increased secretion by the thyroid and various reflex phenomena. The indication for the use of quinine being therefore the necessity for the exhibition of a vaso-constrictor.

Attempts/.

* Jannin, Rev. Med. de la Suisse, 20th May, 1899.

* Journal de Med. Interne, Dec. 15th, 1898.

Attempts have been also made to allay the symptoms of the disease by means of external medication. *Dr Murray of Newcastle has experienced considerable success in several cases by the inunction of the red iodide of mercury to the thyroid gland, the immediate object being the reduction in size of the gland. A small piece of the ointment the size of a pea is rubbed on the gland once daily until the skin becomes too tender for further application. With the reduction in size of the gland, various symptoms have been found to abate considerably. Counter-irritation with various other preparations of iodine have also been attended with some success.

*Professor Pitres of Bordeaux has advocated as treatment, the injection of a solution of iodoform in ether into the body of the gland at intervals of eight days. The result of this treatment has not been followed up. The administration of thyroid extract has very curiously in some cases produced a beneficial effect, and in a few isolated instances, it has been claimed to have practically cured the disease. In the great majority of cases, however, in which large doses of this remedy have been given, it has been found that many, if not all of the symptoms/

* 19th Century of Medicine, Vol. IV., p. 803.

* Lancet 1899, p. 516.

toms have been intensified. We know that thyroid feeding is the only treatment of any avail in Myxoedema, and Myxoedema is the exact antithesis of Exophthalmic Goitre in all its symptoms. Then, surely to treat both diseases by means of the same powerful drug must be altogether wrong. The true explanation of the apparent benefit from thyroid feeding in Graves' Disease is a matter of some difficulty. Perhaps the benefit derived is more apparent than real, or it may be a matter of coincidence. Dr Murray^{*} has found little difference either way from this form of treatment and argues that the thyroid in Exophthalmic Goitre is secreting so enormously that a little more or a little less will make no appreciable difference to the individual.

Thymus gland substance has also been given in Graves' Disease but with only doubtful effect. Some authorities have procured some degree of beneficial effect from its use, while others again, such as Dr M'Kenzie^{**} have not noticed any appreciable benefit whatever. M'Kenzie concludes that it produces no specific action in the disease, either on the heart, goitre, or on the exophthalmos, but that it may produce a good effect on the general condition.

Treatment/

* Lancet, 1893. p. 1223.

** American Journal of Medical Science, February, 1897.

Treatment by extract of supra-renal body has also received attention. This extract is said to have an effect upon the system almost antagonistic to that of thyroid extract. It has been claimed by some who have tried the remedy that some amelioration of symptoms has been procured by its use, but so far as the literature on the subject goes at the present day, its beneficial effect in Graves' Disease is only problematical.

Treatment by means of electricity has received a deal of attention from some observers and has been especially advocated by Vigoroux and Charcot. Some physicians in this country are of opinion that this is the best form of treatment yet introduced. It is recommended that a constant current be applied to the neck for five minutes at each sitting, and an interrupted current be applied over the praecordia for a like period. The faradic current may be increased in strength as the patient becomes used to the treatment. To procure the greatest benefit possible this treatment must be vigorously applied at special intervals over a long period. Appreciable benefit has been produced from its use, and is certainly worth a trial, if the patient can be induced to continue the treatment for long periods. Vandey* has used the electric treatment with success. The/

* Electro-Therapeutics. Rochwell Medical Annual, 1899.

The object seems to be the partial or complete obliteration of small vessels and retraction of the tissues of the gland, and thereby glandular atrophy. This would therefore lessen the tendency to hyperthyroidation, and suppress toxic secretions.

For the diminished expansion of the chest Dr Bryson herself has advocated the use of the instrument known as Taylor's respirator. This apparatus works by means of steam. In this way a tonic action is produced on the muscles of the chest without fatigue to the patient. The power of expansion is in this way increased.

Surgical treatment in Graves' Disease has of late years received a great deal of attention. Surgical interference may become necessary in an occasional case where there is danger to life from the enlarged thyroid pressing on the trachea. Division of the isthmus will generally be found to give great relief in most cases, but it has been recorded that this operation was not sufficient to relieve the dyspnoea. If no relief follows the section of the isthmus, then the best operation is probably the removal of one half of the whole gland. This operation may be undertaken with a double purpose. It not only relieves the immediate symptoms of pressure, but also there is hope that it may be the best surgical/

ical means of ameliorating the urgent symptoms of the disease. This mode of treatment, moreover, is quite justifiable where there is probability of a sudden death, as has occasionally occurred. A case is on record in which from long-continued pressure on the trachea, the cartilaginous rings became softened and a sudden caving-in of the part under the thyroid caused an immediate death from suffocation. When cysts occur in the gland they should be enucleated. Simple tapping has been resorted to in some cases, but it has been found that the cysts soon fill again, thus necessitating frequent repetitions of the operation. A few cases are on record as being greatly benefited by the removal of a cyst. In those cases where it is decided to interfere surgically authorities are still divided as to the best means of doing so. Statistics of operation at the present time are somewhat unreliable, but so far as it goes one is led to believe that a decided amelioration of symptoms, if not a complete cure, may be looked for in about 70% of all cases operated upon. In some instances a decided change for the better has been noticed, immediately after the operation, while in others a considerable time may elapse before any appreciable change takes place. Kocher advised at one time very/

very strongly the operation of ligature of the arteries of supply to the gland, thus causing an atrophy and consequently a diminished secretion from the gland. This operation in most cases is a simple one and on that account recommends itself. It can be carried out even in those cases, and which perhaps form a large proportion, where ^{considerable} debility exists.

Excision of one lobe of the thyroid gland has also found favour with some in late years. This operation is a rather severe proceeding and can only be recommended in suitable cases. Further, it is one that should only be undertaken after such means as drugs, and perhaps the electrical treatment have failed to have an effect upon the disease. Formerly alarming symptoms were apt to follow this operation, such as severe aggravation of all the symptoms of exophthalmic goitre, and considerable collapse.

It is possible that this might be produced from the effects of a severe operation upon a debilitated and weak subject, with probably a weak and flabby heart. This, however, is in all probability not the true cause. It is more likely to be the result of the absorption by the wound of a toxic dose of thyroid secretion exuding from the cut surface of the gland.

Schultz/

Schultz* has published a record of twenty cases treated by partial excision of the thyroid gland. In eighteen of these he found the results very satisfactory. The results support the view that the thyroid gland is responsible for the clinical features of the disease, as the operation was followed generally by slowing of the pulse, diminution of the exophthalmos, and improvement in the condition of the patient. The portion of gland left behind became smaller. Schult, however, does not recommend the operation until treatment by medicinal means has failed to relieve the patient.

Stokes** believes also that partial removal of the gland is likely to lead to beneficial results if not to absolute cure of the disease.

Many other surgeons also have published cases in which excision of part of the thyroid has given lasting good results. The operation therefore may be with comparative safety recommended in those cases in which other treatments have failed to produce a beneficial effect.

Pollard and Lake*** believe that there are two forms of the disease, one in which the enlargement of the thyroid is the leading feature, and another in/

* Centralbl. f. Chirurgie, Leipzig, 19th Oct. 1901.

** British Medical Journal, October 29th, 1898.

*** British Medical Journal, October 14th, 1899.

in which there is no such enlargement. In the former they recommend partial excision of the gland, and in the latter, excision of the sympathetic on both sides of the neck. The same authorities also believe that if the sympathetic cervical ganglia be first of all removed, the operation of partial thyroidectomy will be attended with less danger. Jaboulay* is also of the same opinion and practises the removal of the superior sympathetic before undertaking the more serious operation of thyroidectomy. Section of the cervical sympathetic above has also been strongly recommended by some. This operation has been carried out on one side only and also on both sides. The results have, to a certain extent, been encouraging, but in a great many cases little benefit has accrued from the proceeding. Complete removal of the cervical sympathetic ganglia has also been practised. The best results from this form of surgical treatment have perhaps been obtained by Jonnesco**. Out of ten cases in which he completely excised the sympathetic from both sides of the neck, six he claims were completely cured, while four were greatly benefited.

Eshner/

* Press Med., February. 12th, 1898.

** Centralbl. f. Chir. Leipzig. 1897.

Eshner and Jonnesco* believe that total and bilateral excision of the cervical sympathetic is the best operation and that lasting results are generally obtained. After carefully studying the data to be found of the results of those various operations, it is a matter of some difficulty to know which mode of surgical procedure will be the most likely to result in benefit to any given case of Graves' Disease. Looking at the question from the point of view of the pathology which is most generally believed at the present day; namely, that whatever be the primary cause of the disease the immediate cause is in all probability an excess of secretion thrown into the blood stream by the thyroid; the best operation would be one which would tend in some way to diminish that secretion.

The operation which would immediately have this effect and which most readily occurs to the mind, is that of partial thyroidectomy. This proceeding, however, is one not lightly to be undertaken, as the operation is one of some difficulty and besides in all probability, not every patient is in a fit state of health to undergo it. If the operation were undertaken more early in the course of the disease and more cases treated in this way, the statistics of/

of results from it would, in all probability, be more encouraging than that of any other surgical proceeding.

It is rather curious to note that such a substance as pig's bile, administered partly by hypodermic injection, has been tried as a curative agent in Graves' Disease. The results were decidedly good, as far at least as one case was concerned*. It is probable that, as the observer admits himself, the benefit obtained was the result chiefly of the action of the bile taken by the mouth, and therefore a general benefit.

As has already been stated, a poison absorbed from the intestinal canal has been blamed as a probable cause of Graves' Disease. Treatment has been directed to remedy this by intestinal antiseptics. Dr Thompson of New York** is of the belief that ptomaines absorbed from the intestinal tract may in all probability be the cause of the disease and directs his attention to prevent this by the administration of such intestinal antiseptics as Phenol Bismuth, Naphthol Bismuth, Salol or Bismuth Salicylate. He also directs attention to the diet and allows chiefly milk, eggs, fish, and stale bread. Meat he considers a fruitful source of the poison and advises that it be withheld altogether. From all that has/

* Lancet, August, 26th, 1899.

** Americal Journal of Medical Science, Feb. 1897.



has been advocated therefore in the treatment of Graves' Disease, it will be seen at once that authorities are still greatly divided as to the best mode of treatment of this malady. It would appear that certain cases adapt themselves to certain methods of treatment. The mild and early case should probably be at first treated on general medical principles, attention being directed to residence at a high altitude (at least 500 feet above the sea) and on no account on a limestone formation. They should receive a liberal supply of easily digested food, much rest and suitable tonic treatment. All forms of excitement should be carefully guarded against. Along with this one of the many special lines of treatment is to be adopted, and being once entered upon should be pushed energetically and patiently.

The more severe methods of surgical treatment one is still inclined to withhold as a measure which may be adopted if others fail, and if there is any immediate call for such owing to an early prospect of death from one cause or other.

There is perhaps no disease in which patience and perseverance, both on the part of the patient and physician are more necessary than in Graves' Disease.